

High-Dose Carmustine, Etoposide, and Cisplatin for Autologous Stem Cell Transplantation with or without Involved-Field Radiation for Relapsed/Refractory Lymphoma: An Effective Regimen with Low Morbidity and Mortality

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ABSTRACT

Over a 10-year period (January 1993 to October 2002), 101 relapsed or refractory non-Hodgkin lymphoma patients were treated at our center with high-dose chemotherapy and autologous transplantation. The median patient age was 54 years (range, 25-70 years). Thirty-two patients had indolent (low-grade), 42 had aggressive (intermediate-grade), and 27 had very aggressive (high-grade) non-Hodgkin lymphoma. Thirty-six patients had primary refractory disease, 20 had a chemoresistant relapse, 35 patients had a chemosensitive relapse, and 10 patients were "initial high risk" patients. The median number of prior chemotherapy regimens was 2 (range, 1-5). The preparative regimen (BEP) was bischloroethylnitrosourea (BCNU) 600 mg/m², etoposide 2400 mg/m², and Platinol (cisplatin) 200 mg/m² given intravenously over 5 days. Within 3 weeks before transplantation, 70 patients received involved-field radiotherapy (IFR) 20 Gy to sites of currently active (>2 cm) or prior bulky (>5 cm) disease. Most patients (n = 93) received mobilized peripheral blood stem cells (median CD34⁺ cell dose, 6.7 × 10⁶/kg). Median neutrophil (>500/μL) and platelet (>20 000/μL, untransfused) recoveries were 11 days (range, 7-19 days) and 14 days (range, 7-36 days), respectively. At a median follow-up of 41 months (range, 4 to 118 months) for survivors, Kaplan-Meier 5-year probabilities of overall survival (OS) and disease-free survival (DFS) were 58.6% and 51.1%, respectively. Four patients (4%) died within 30 days of stem cell infusion (1 pulmonary embolism, 2 septicemias with multiorgan failure, and 1 progressive lymphoma). Two patients (2%) developed interstitial pneumonitis most likely secondary to high-dose BCNU. Three cases (3%) of secondary acute myelogenous leukemia occurred. On multivariate analysis, age (<60 or ≥60 years), histologic grade (low versus intermediate or high), the use of IFR, and chemotherapy response at baseline did not affect OS or DFS. Of 70 patients given IFR, 27 relapsed: 10 (37%) within and 17 (63%) outside the radiation field. The use of IFR did not affect either OS or DFS, probably because IFR was offered to patients with bulky or chemoresistant disease. BEP with or without IFR is a highly effective and well-tolerated regimen in the relapsed/refractory lymphoma setting. It has low morbidity and transplant-related mortality and a low incidence (3%) of posttransplantation malignancy.

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KEY WORDS

Non-Hodgkin lymphoma • Autologous transplantation • BCNU • Cisplatin • Etoposide

INTRODUCTION

Non-Hodgkin lymphomas (NHL) represent a class of chemosensitive neoplasms for which approximately 40% to 50% of patients with intermediate- and high-grade disease achieve disease-free survival at 4 to 5 years after conventional chemotherapy [1]. A randomized study validated the superiority of high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) over conventional salvage chemotherapy in the setting of chemosensitive disease relapse [2]. In patients with primary refractory NHL, the disease-free survival (DFS) after HDC and ASCT is approximately 30% to 35% [3]. Disease relapse, most often at sites of prior involvement, accounts for most treatment failures after HDC and ASCT [4,5]. This finding has prompted an interest on the part of investigators in the use of involved-field radiotherapy (IFR) as an adjunct to HDC and ASCT to minimize the local relapse rate. Although multiple radiation-based and chemotherapy-alone conditioning regimens have been incorporated into the transplant setting, no randomized studies have demonstrated the superiority of one regimen over any other [6,7]. Transplant-related complications, including pulmonary toxicity and secondary myelodysplastic syndromes (MDS), also may account for morbidity and mortality after ASCT [8,9]. We reported previously on the promising results of our phase I to II multi-institutional trial investigating a novel high-dose chemotherapy-alone conditioning regimen, BEP (bischloroethylnitrosourea [BCNU], etoposide, and Platinol [cisplatin]), in the relapsed and refractory lymphoma setting [10]. In this report, we describe our single-institution phase II experience in 101 relapsed/refractory NHL patients subsequently undergoing ASCT with this BEP regimen (usually in conjunction with IFR) during a 10-year period (1993-2002), with a special emphasis on the regimen efficacy and low incidence of transplant-related complications.

PATIENTS AND METHODS

Patients

Between January 1993 and October 2002, 101 patients with relapsed/refractory disease or high-risk NHL patients were treated with HDC and ASCT. Patients were treated within the confines of protocols approved by the Institutional Review Board at the University Hospitals of Cleveland, Comprehensive Cancer Center of the Case Western Reserve University. Patients gave written, informed consent to participate. Subjects were eligible if they had primary refractory disease (failure to achieve at least a partial remission after 2 cycles of front-line chemotherapy or failure to achieve a complete remission after 6 cycles of front-line chemotherapy) or relapsed disease. Patients with relapsed disease were further classified as having either a chemosensitive relapse

(>50% reduction in measurable disease after conventional salvage chemotherapy) or a chemoresistant relapse (<50% reduction in measurable disease after conventional salvage chemotherapy). NHL patients also were eligible if they had attained their first complete or near-complete remission after induction chemotherapy but were deemed to be at high risk for a relapse according to criteria described in the International Prognostic Index scoring system [11]. NHL was classified according to the Working Formulation [12] and the World Health Organization classification [13]. Cases of mantle cell lymphoma were assigned to the low-grade NHL group for statistical analysis. Patients were required to have an Eastern Cooperative Oncology Group performance status of ≤ 2 , absence of active infection, and adequate cardiac, pulmonary, hepatic and renal function. Specifically, patients were eligible if their left ventricular ejection fraction was at least 40% on multiple-gated acquisition scan, their corrected diffusing capacity of the lung for carbon monoxide and forced expiratory volume in 1 second were at least 60% of predicted, serum direct bilirubin was ≤ 2.0 mg/dL, and calculated creatinine clearance was at least 60 mL/min.

Treatment

Most patients received salvage chemotherapy before transplantation, most often a regimen based on cisplatin, cytosine arabinoside, and dexamethasone, with or without etoposide [14,15]. Before the transplantation, 70 patients also received IFR to sites of currently active (tumor diameter exceeding 2 cm) or previous bulky (defined as a tumor site exceeding 5 cm in diameter at initial presentation) disease. IFR was not administered unless at least 90% of all active and bulky disease could be treated. Treatment was administered in 2-Gy fractions once daily for up to 10 treatments in the 14 days preceding the initiation of the HDC preparative regimen. Some of the earlier patients received harvested autologous bone marrow mononuclear cells, whereas most of the patients treated after 1994 received mobilized peripheral blood stem cells. The regimen most commonly used to accomplish stem cell mobilization was cyclophosphamide 4 g/m² infused intravenously over 6 hours and granulocyte colony-stimulating factor (filgrastim, Neupogen; Amgen, Thousand Oaks, CA) 10 μ g/kg/d subcutaneously [16-18]. Twelve patients received etoposide in addition to cyclophosphamide, administered at 200 mg/m² intravenously over 3 hours daily for 3 days.

Preparative Regimen and Stem Cell Infusion

High-dose therapy (schema outlined in Table 1) comprised BCNU 200 mg/m² in 500 mL of 5% dextrose water given intravenously over 2 hours daily for 3 days, etoposide 800 mg/m² administered as a native

Table 1. High-Dose Chemotherapy Schema

Variable	Day									
	-7	-6	-5	-4	-3	-2, -1	-0	+7 to +13	+14 to +20	
BCNU 200 mg/m ² IV (600 mg/m ²)		X	X	X						
Etoposide 800 mg/m ² IV (2400 mg/m ²)		X	X	X						
Cisplatin 40 mg/m ² IV (200 mg/m ²)	X	X	X	X	X					
Rest						X				
Stem cell infusion							X			
Prednisone 2 mg/kg/d PO								X		
Prednisone taper									X	

IV indicates intravenously; PO, by mouth.

drug intravenously during a 4-hour period via an infusion pump daily for 3 days [19], and cisplatin 40 mg/m² in 250 mL of 3% saline infused intravenously over a 3-hour period preceded by intravenous furosemide and followed by mannitol daily for 5 consecutive days. Cryopreserved autologous bone marrow or blood stem cells were reinfused 72 hours after completion of the preparative regimen.

Supportive Care

All patients were treated in high-efficiency particulate air-filtered isolation rooms during the period of granulocytopenia. Patients who underwent transplantation after 1994 were treated with daily recombinant granulocyte colony-stimulating factor 5 µg/kg or granulocyte-macrophage colony-stimulating factor (sargramostim, Leukine; Berlex, Seattle, WA) 250 µg/m² subcutaneously starting the day of transplantation and continuing until an absolute neutrophil count of >500/µL was reached. After transplantation, patients received standard supportive care for the treatment of neutropenic fevers with broad-spectrum antibacterial drugs (usually a third-generation cephalosporin or an extended-spectrum penicillin combined with an aminoglycoside), with the addition of amphotericin B or fluconazole for persistent fevers beyond 72 to 96 hours. Acyclovir was administered at 250 mg/m² intravenously every 8 hours from the day of stem cell reinfusion until neutrophil recovery. Gastrointestinal adverse effects, mucositis, and esophagitis were managed according to standard supportive care practice guidelines. Additionally, patients were treated with prednisone 2 mg/kg/d by mouth from day 7 until day 13 after transplantation, followed by a rapid taper over the subsequent week to minimize the development of interstitial pneumonitis secondary to high-dose BCNU. Patients were transfused with irradiated blood products to maintain a platelet count >10 000/µL and hemoglobin >10 g/dL. Toxicities were graded according to the common toxicity criteria of the National Cancer Institute.

Statistical Methods

Overall survival (OS) was measured from the date of transplantation to the date of death and was cen-

sored at the date of last follow-up for survivors. DFS was measured from the date of transplantation to the date of death or relapse and was censored at the date of last follow-up for survivors without relapse. The probability of OS and DFS was estimated by the Kaplan-Meier method [20]. The log-rank test was used to assess differences in outcome between/among groups. Univariate analyses were performed with the log-rank test. Factors potentially predictive of OS were entered into a multivariate analysis by using the Cox proportional hazards model [21]. The factors included in the Cox model were age, histologic grade, use of IFR, and chemotherapy response at baseline. All tests were 2 sided, and *P* values ≤0.05 were considered significant.

RESULTS

Patient Characteristics

Patient characteristics are outlined in Table 2. A total of 101 patients (68 men and 33 women) received autografts during a 10-year period. Of these subjects, 32 had low-grade NHL (including 7 patients with mantle cell lymphoma), 42 had intermediate-grade NHL, and 27 had high-grade NHL (including 5 patients with Burkitt lymphoma). The median age was 54 years (range, 25-70 years), and 16 patients (16%) were older than 60 years. Forty-seven (46.5%) patients had bone marrow involvement at diagnosis. The mean serum lactate dehydrogenase at the time of transplantation was 413 U/L (range, 112-2435 U/L). Thirty-six patients (35.6%) had primary refractory disease, 35 patients (34.7%) had a chemosensitive relapse, 22 patients (19.8%) had a chemoresistant relapse, and 10 patients (9.9%) were patients with high-risk disease who underwent transplantation in the first complete or near-complete remission. The median number of chemotherapy regimens before transplantation was 2 (range, 1-5). Seventy patients (69.3%) received IFR (20 Gy) to sites of currently active or previously bulky disease, as defined previously. Of the 70 patients who received IFR, 24 (34.2%) received mediastinal radiation. Most patients (93/101; 92%) received mobilized peripheral blood stem cells (me-

Table 2. Patient Characteristics

Variable	IFR Cohort	No-IFR Cohort	All Patients
Total	70	31	101
Male	48	20	68
Female	22	11	33
Median age, y (range)	54 (25-70)	50 (33-66)	54 (25-70)
Mean LDH, U/L	414	419	413
Histology			
Low-grade NHL (+ mantle cell)	17	15	32
Intermediate-grade NHL	35	7	42
High-grade NHL	18	9	27
Median no. prior chemotherapy regimens (range)	2 (1-5)	2 (1-4)	2 (1-5)
Disease status at transplantation			
Primary refractory	29	7	36
Chemosensitive relapse	22	13	35
Chemoresistant relapse	17	3	20
Primary high risk	2	8	10

LDH indicates lactate dehydrogenase.

dian CD 34 cell dose, $6.7 \times 10^6/\text{kg}$; range, $1.7\text{--}22 \times 10^6/\text{kg}$). Eight patients received unstimulated autologous bone marrow cells (median mononuclear cell dose, $2.3 \times 10^8/\text{kg}$; range, $1.9\text{--}3 \times 10^8/\text{kg}$).

Outcomes

At a median follow-up of 41 months for survivors (range, 4–118 months), the Kaplan-Meier 5-year probability of DFS and OS for the entire group was 51.1% and 58.6%, respectively (Figures 1 and 2). Tables 3 and 4 (univariate analyses) show that neither age (<60 years versus ≥ 60 years) nor the use of IFR nor lymphoma grade (low versus intermediate or high) affected OS or DFS; there was a trend, however, toward a shorter DFS for patients with low-grade NHL ($P = .204$).

Disease Status

When stratified according to disease responsiveness (primary refractory disease, chemoresistant relapse, chemosensitive relapse, or patients with high-

risk disease who underwent transplantation in first complete remission), there was no significant difference in the DFS or OS in each of these groups (Figures 3 and 4). Of note, this regimen was very active in the group of patients with primary refractory disease; the 5-year DFS and OS were 54.1% and 63%, respectively, comparable to those in patients with chemosensitive relapsed disease. When the group of 10 high-risk patients who underwent transplantation in first complete remission was compared with the other 3 groups collectively, there was a statistically significant improvement in OS and DFS; all 10 patients remain alive and disease free at a median follow-up of 18 months ($P = .01$).

Histology

For NHL, OS for the 32 patients with low-grade disease did not differ compared with that for the 69 subjects with intermediate- or high-grade disease (62.5% versus 56.3%; $P = .593$), although there was a

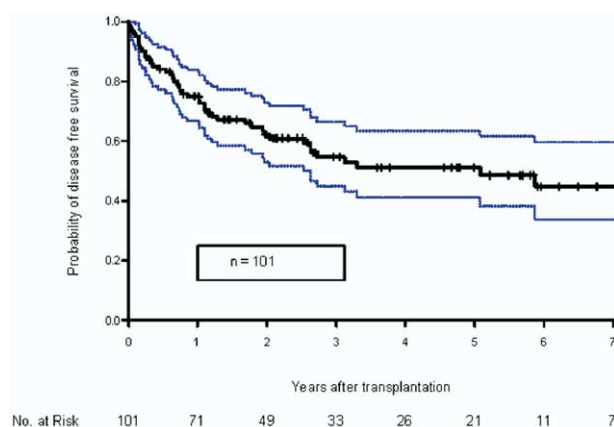


Figure 1. Kaplan-Meier probability of disease-free survival for all patients.

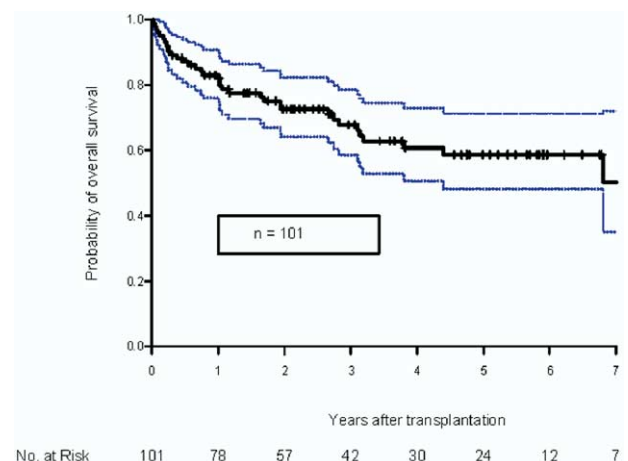


Figure 2. Kaplan-Meier probability of overall survival for all patients.

Table 3. Kaplan-Meier Estimation of Disease-Free Survival Function for Various Groups

Factor	n	Survival at 1 y	Survival at 3 y	Survival at 5 y	Survival at 7 y	P Value
All patients	101	74.9	54.6	51.1	44.8	
Age (y)						
<60	85	73.8	52.3	52.3	45.3	.845
≥60	16	81.3	65.7	49.2		
IFR						
No	31	72.8	52.9	52.9		.56
Yes	70	75.7	54.2	49.7	41.3	
Grade						
IM/H	69	74.9	60.4	57.9	52.6	.204
Low	32	75	42.7	36.6		
Response to chemotherapy						
Primary refractory	36	77.8	54.1	54.1	54.1	.062
Chemoresistant relapse	20	60	46.8	39	39	
Primary high risk	10	100	100	100		
Chemosensitive relapse	35	73.7	48.4	43	26.9	

IM/H indicates intermediate/high.

trend toward a lower DFS in the low-grade compared with the intermediate-/high-grade group (36.6% versus 57.9%; $P = .204$).

Involved-Field Radiation

Seventy patients received IFR to sites that were previously bulky (>5 cm) or currently active (>2 cm) immediately before the chemotherapy preparative regimen was initiated. For these patients, there was no significant difference in OS (54% versus 72.3%; $P = .478$) or DFS (49.7% versus 52.9%; $P = .56$) when compared with the 31 patients who did not receive IFR (Figures 5 and 6). Twenty-seven of the 70 patients treated with IFR relapsed: 10 (37%) relapses occurred within the field of radiation, and 17 (63%) were outside it.

Toxicities

All patients developed neutropenia and thrombocytopenia but engrafted and recovered peripheral

blood counts. Median neutrophil (>500/ μ L) and platelet (>20 000/ μ L, untransfused) recoveries were 11 days (range, 7-19 days) and 14 days (range, 7-36 days), respectively. For the 70 patients who received IFR, the median neutrophil recovery was 10 days (range, 7-19 days), compared with 11 days (range, 7-19 days) for the subjects who did not receive IFR. Platelet recovery was also similar in the 2 cohorts: 14 days (range, 8-36 days) in the IFR group versus 15 days (range, 7-26 days) in the absence of IFR. Six (6%) of the 101 patients developed acute renal failure after HDC. Four of these cases occurred in the context of septicemia and multisystem organ failure and hypotension; in 2 cases, no other underlying cause of the renal failure was identified (possibly secondary to high-dose cisplatin). Four patients recovered renal function after hemodialysis support, whereas 2 patients died as a result of septicemia and multisystem organ failure.

Four patients died within 30 days of stem cell rein-

Table 4. Kaplan-Meier Estimation of Overall Survival Function for Various Groups

Factor	n	Survival at 1 y	Survival at 3 y	Survival at 5 y	Survival at 7 y	P Value
All patients	101	83	67.8	58.6	50.3	
Age (y)						
<60	85	83.4	67.2	60.1	51.5	.837
≥60	16	81.3	73.1	56.9		
IFR						
No	31	83.5	72.3	72.3		.478
Yes	70	82.9	65.9	54	54	
Grade						
IM/H	69	80.8	64.1	56.3	56.3	.593
Low	32	87.5	75.7	62.5		
Chemotherapy response						
Primary refractory	36	86.1	71.8	63	63	.116
Chemoresistant relapse	20	70	55.1	47.3	47.3	
Primary high risk	10	100	100	100		
Chemosensitive relapse	35	82.7	60.8	49.1	24.6	

IM/H indicates intermediate/high.

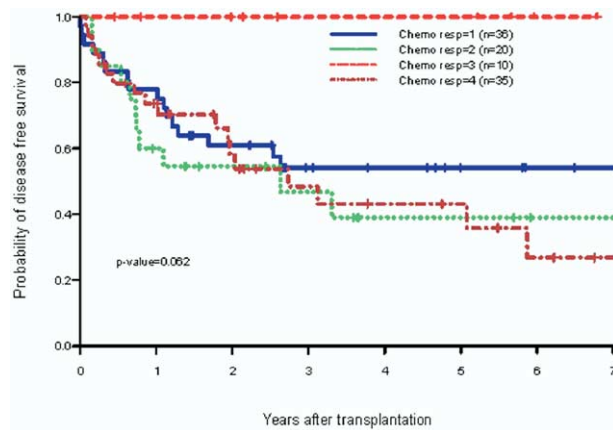


Figure 3. Kaplan-Meier probability of disease-free survival according to disease status: primary refractory disease (n=36), chemoresistant relapse (n=20), chemosensitive relapse (n=35), and high-risk first complete remission (n=10).

fusion (transplant-related mortality of 3.5%); 2 of these patients received IFR before the transplantation. One patient developed a fatal pulmonary embolus, 2 subjects died as a result of septicemia and multisystem organ failure (1 with herpes simplex virus-1 fulminant hepatic necrosis and sepsis), and 1 patient died of progressive lymphoma. Grade 3 or 4 mucositis was observed in 9 (29%) of 31 patients not receiving IFR and in 40 (57.1%) of 70 patients receiving IFR ($P = .009$). Nine episodes of new-onset atrial fibrillation were observed during the course of the transplantation, all of which occurred in the context of electrolyte imbalance (hypokalemia, hypomagnesemia, or their combination), despite aggressive daily monitoring of serum electrolytes. Culture-positive bloodstream infections were noted in 9 (29%; 8 bacteremias and 1 fungemia) of the 31 patients who did not receive IFR and in 13 (18.6%; 10 bacteremias and 3 fungemias) of the 70 patients treated with IFR ($P = .24$).

A low incidence of interstitial pneumonitis was noted

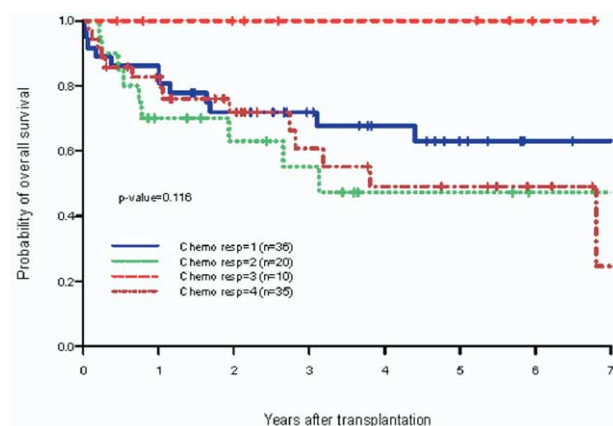


Figure 4. Kaplan-Meier probability of overall survival according to disease status: primary refractory disease (n=36), chemoresistant relapse (n=20), chemosensitive relapse (n=35), and high-risk first complete remission (n=10).

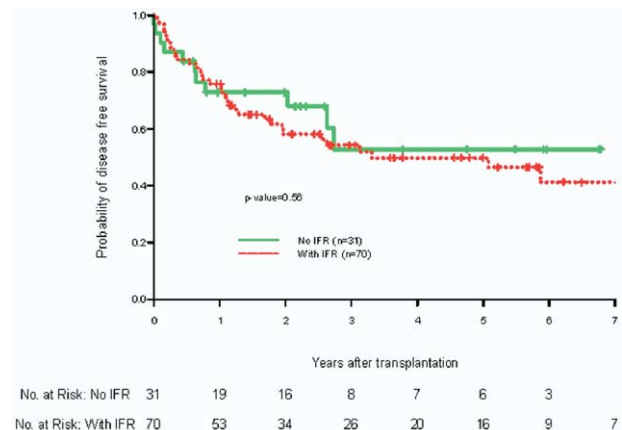


Figure 5. Kaplan-Meier probability of disease-free survival according to use of IFR (n=70) versus no IFR (n=31).

(2/101 patients; 2%). Neither of these patients had received radiation therapy to the mediastinum. The diagnosis of interstitial pneumonitis was made clinically by exclusion of other causes of pulmonary pathology. These patients presented with dyspnea and hypoxemia within 120 days of transplantation and had radiologic evidence of interstitial or perihilar infiltrates. Infectious etiologies and pulmonary embolism were excluded by bronchoscopic alveolar lavage and spiral computed tomography or ventilation/perfusion scanning, respectively. Both patients had a restrictive pattern on pulmonary function testing, and one had an open lung biopsy that revealed a pattern of diffuse interstitial fibrosis. Both subjects were treated with corticosteroids and improved; one, however, remains dependent on supplemental oxygen at 40 months after transplantation.

Secondary Malignancies

At the time of last follow-up, no secondary solid tumors had occurred in any patient in this series. Three cases of secondary MDS/acute myelogenous

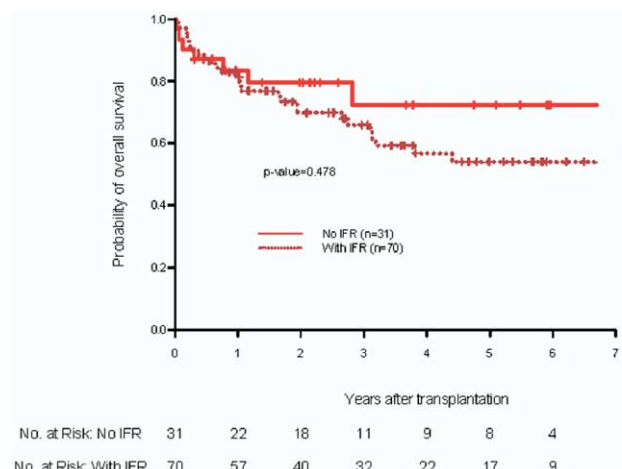


Figure 6. Kaplan-Meier probability of overall survival according to use of IFR (n=70) versus no IFR (n=31).

leukemia (AML) were noted. The first patient initially had stage IIA lymphoblastic lymphoma and was treated according to the Coleman regimen [22] with cyclophosphamide, doxorubicin, vincristine, prednisone, L-asparaginase, methotrexate, and intrathecal cytosine arabinoside. She also received 20 Gy of IFR to the neck and mediastinum and subsequently underwent an autograft in first complete remission. Ten months later, she developed secondary AML (trisomy 7, trisomy 10, and t[5;13]). She underwent a myeloablative peripheral blood sibling-matched allograft but died 2 months later secondary to hepatic veno-occlusive disease. The second patient had an initial diagnosis of stage IV follicular small cleaved NHL, received 3 prior chemotherapy regimens, and was given IFR to the right cervical and periaortic nodes before transplantation. She developed secondary AML 55 months after transplantation. She received a reduced-conditioning sibling-matched allogeneic stem-cell transplant and remains in complete hematologic remission 12 months after the second transplantation. The third patient had long-standing low-grade NHL; 9 years after diagnosis, she underwent an autograft and exposure to numerous cytotoxic regimens. She developed secondary AML 4 years after autografting for NHL, was induced into a complete remission with high-dose cytarabine, and remains well 19 months after a reduced-conditioning sibling-matched allogeneic peripheral blood stem cell transplantation.

DISCUSSION

We previously reported our phase I and II multi-institutional pilot data with the BEP chemotherapy conditioning regimen in relapsed/refractory NHL and Hodgkin disease [10]. In the current report, we present our single-institution phase II data on 101 subsequent relapsed, refractory, or high-risk NHL or Hodgkin disease patients who underwent ASCT with the BEP regimen, usually in conjunction with IFR, as described. At a median follow-up of 41 months for survivors, the 5-year Kaplan-Meier probabilities of DFS and OS (51.1% and 58.6%, respectively) compare favorably with several of the larger reports in the literature with a variety of total body irradiation(TBI)-containing and non-TBI-containing regimens [23–28]. With a multivariate analysis, factors such as age (<60 years versus ≥ 60 years), grade of lymphoma (low versus intermediate or high), use of IFR, and chemotherapy response at baseline did not affect OS or DFS. We did note a lower DFS trend for 32 patients with low-grade NHL (36.6% versus 57.9%; $P = .204$) when compared with 69 patients with intermediate-/high-grade NHL; this finding could be ex-

plained, in part, by the natural history of an increased tendency of low-grade NHL to relapse. Additionally, for statistical analysis, 7 patients with mantle cell NHL were included in the low-grade NHL group; at last follow-up, all 7 had relapsed, and 5 had died.

Of note, contrary to many reports in the literature, disease chemosensitivity did not seem to affect DFS and OS in our study. For our group of 36 patients with primary refractory disease, the 5-year DFS and OS were 54.1% and 63%, respectively, which did not differ significantly compared with patients who had chemosensitive relapse. This result compares favorably to data generated from 85 patients with primary refractory NHL reported by Kewalramani et al. [25]. Further, data from the Autologous Blood and Marrow Transplant Registry report [3] describe 184 patients with NHL primary refractory disease who underwent autografts and had 5-year probabilities of DFS and OS of only 31% and 37%, respectively. Although our regimen seems to be particularly promising in this patient population, the results, similarly, are based on a retrospective analysis and need to be reproduced prospectively in a larger cohort of patients.

Our conditioning regimen was well tolerated and associated with a surprisingly low incidence of interstitial pneumonitis (2/101; 2%). BCNU pulmonary toxicity, potentially related to the inhibition of glutathione reductase in alveolar macrophages [29], seems to be dose related, with a 28% incidence at 600 mg/m² compared with 4% at 450 mg/m² [30]. Jones et al. [31] reported pharmacokinetic data on 38 breast cancer and NHL autotransplant recipients given BCNU 600 mg/m² (infused in 1 day), cyclophosphamide 1875 mg/m², and cisplatin 165 mg/m². Twenty (53%) of the 38 patients developed pulmonary injury. Twelve affected subjects had BCNU area under the curve values >600 $\mu\text{g/mL/min}$, whereas only 2 (11%) of 18 patients who did not develop lung injury had values above this cutoff ($P < .03$); eg, organ dysfunction arose in 12 (86%) of 14 patients with a BCNU area under the curve >600 $\mu\text{g/mL/min}$. Although we infused an identical BCNU dose (600 mg/m²), this agent was administered in divided doses over 3 days; it is reasonable to speculate that our patients had lower peak BCNU concentrations. Additionally, given the data for the benefit of early treatment with corticosteroids to attenuate the chemotherapy-induced decline in the diffusing capacity of the lung for carbon monoxide [32], we routinely treated all our patients with prophylactic corticosteroids (prednisone 2 mg/kg) from days 7 through 14. This approach, in part, may account for the relatively low incidence of interstitial pneumonitis we observed. Of interest, other investigators who substituted high-dose lomustine in place of BCNU in combination with cyclophosphamide and eto-

poside in HDC regimens reported a persistently high incidence (63%) of interstitial pneumonitis [33].

The incidence of secondary MDS/AML in this study was low (3/101 patients; 3%). Multiple studies in the literature have addressed the issue of posttransplantation MDS/AML in NHL patients and have described a 6% to 12% incidence rate. Some of the predictive pretransplantation and transplantation-related risk factors include older patient age, a lower dose of infused hematopoietic progenitors, prior fludarabine or alkylator chemotherapy, stem cell mobilization with an etoposide-containing regimen, prior radiotherapy, an increased interval from diagnosis to transplantation, lower platelet count at or before transplantation, and lymphomatous bone marrow involvement [34-39]. In a recently published Autologous Blood and Marrow Transplant Registry report on 56 secondary MDS/AML patients within a cohort of 2739 NHL/Hodgkin disease patients receiving autotransplants, a TBI dose of 13.2 Gy significantly increased leukemia risks (relative risk, 4.6; $P = .03$), whereas a 12-Gy dose did not seem to increase the secondary leukemia risk (relative risk, 1.3, $P = .48$) above that seen with non-TBI regimens [12]. Our reported incidence of secondary MDS/AML is lower than that observed in other published studies, for unclear reasons.

The role and benefit of IFR in the transplant setting is complex [40]. although some studies have demonstrated improved DFS in patients with bulky disease or improved local control of irradiated sites [28,41,42], no study has convincingly demonstrated improved OS in irradiated patients. Additionally, multiple investigators caution about increases in hematologic toxicity [43], pulmonary morbidity [44], transplant-related MDS/AML, and transplant-related mortality [45] in patients receiving IFR. Seventy patients on our protocol were treated with IFR to previously bulky or currently active disease sites. IFR did not seem to delay time to hematopoietic recovery after transplantation: the median time to neutrophil recovery $>500/\mu\text{L}$ was 10 and 11 days and the median time to platelet recovery $>20\,000/\mu\text{L}$ (untransfused) was 14 and 15 days when comparing irradiated versus nonirradiated patients, respectively. Two patients developed interstitial pneumonitis in our study; neither of these had received prior mediastinal irradiation. Two of 3 cases of secondary AML occurred in patients who had received prior IFR. Of the 70 patients treated with IFR, 27 relapsed: 10 (37%) within and 17 (63%) outside the radiation field. In our study, the 5-year DFS for the 70 patients who received IFR was no different from that for the 31 patients who did not receive radiation (49.7% versus 52.9%; $P = .56$). Of the 70 patients who received IFR, 41% had primary refractory disease and 24% had a chemoresistant relapse, compared with 22% with primary refractory disease and 10% with chemoresistant relapse among the 31 patients who did not receive IFR. Although

these comparisons did not reach statistical significance ($P = .10$; data not shown), there was undoubtedly a trend toward a higher proportion of patients with primary refractory disease and chemoresistant relapses in our IFR cohort. Hence, the apparent lack of benefit of IFR must be interpreted with caution in light of this inherent selection bias of offering IFR to patients with bulky or chemoresistant disease.

This single-institution report of long-term follow-up with the BEP preparative regimen with or without IFR followed by autologous transplantation for relapsed or refractory NHL and Hodgkin disease demonstrates the treatment to be highly effective and well tolerated, with a low incidence of interstitial pneumonitis compared with other high-dose BCNU regimens. Further, this approach seems to be associated with a low incidence of secondary MDS/AML and seems to be particularly promising in the setting of primary refractory disease.

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